Essential Hypertension

Introduction

Hypertension is a common disorder that affects one-third of all adults in the United States. It is a major risk factor for atherosclerosis, congestive heart failure, and renal failure. The emphasis in this lesson is on reviewing the suspected pathogenesis of hypertension and relating it to the mechanisms that govern the MAP equation. This is the current model of its development, although **essential hypertension**, representing 90% of cases, is known to be a complex, multifactorial disease. We will touch on some of the clinically relevant forms of **secondary hypertension** in our advanced organizer, "Triple Harp Company," but the main focus is on essential hypertension.

The lesson proceeds to discuss what happens when blood vessels are subjected to increases in blood pressure. This is not the regulation of blood pressure discussed in Hemodynamics #4, but the pathologic changes when the MAP is too high. The heart is also subjected to increased afterload and can suffer ventricular changes, which we explore as well. And although pulmonary hypertension is discussed in detail in Pulmonary: Circulation #3: *Pulmonary Hypertension*, we introduce the pulmonary vasculature in this lesson to demonstrate the effects on the right ventricle and compare hypertensive heart disease in the left ventricle vs. the right ventricle.

The goal is to know the suspected mechanism of essential hypertension, the pathological changes in arterioles on histology, and the pathologic changes for ventricular chambers in response to hypertension. Finally, we conclude with a brief review of secondary hypertension.

Pathogenesis of Essential Hypertension

Hypertension is likely a multifactorial disorder that results from the cumulative effects of multiple genetic polymorphisms and interactions between environmental factors. Let's start off with the MAP equation and what hypertension is NOT caused by.

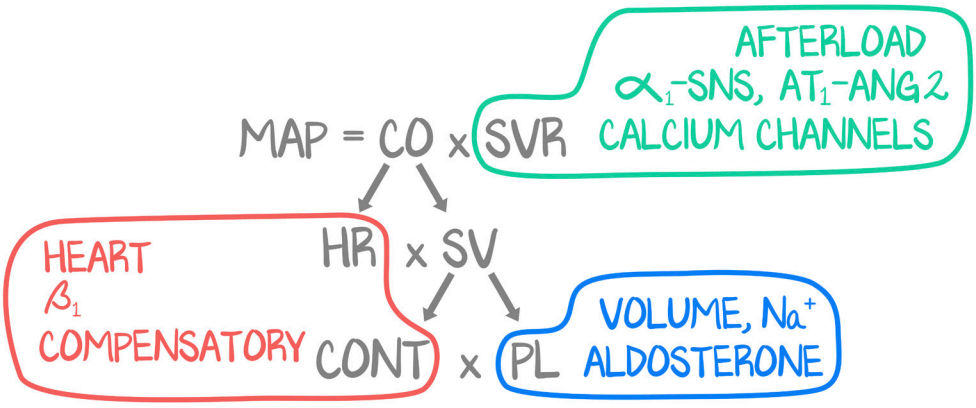

Figure 5.1: Mean Arterial Pressure Equation
The MAP is the product of cardiac output and systemic vascular resistance. Systemic vascular resistance is now renamed to afterload, how much the heart has to push against with each heartbeat. Cardiac output is the product of heart rate and stroke volume. Stroke volume is the product of contractility and preload. Increasing the heart rate, contractility, preload, or systemic vascular resistance will increase the MAP. Pathologic changes resulting in essential hypertension are unrelated to the stimulation of β_1; increased heart rate and contractility are not part of the development of essential hypertension and are compensatory mechanisms for a falling MAP. In essential hypertension, increases in afterload or preload are to blame.

But it isn't that simple, just afterload and preload. We do target both afterload and preload with blood pressure medications to bring down a person's blood pressure, to control the damage hypertension causes to the blood vessels in all organs and the changes it induces in the left ventricle. But so much more than that contributes to elevated blood pressure.

Genetic factors influence blood pressure regulation, as evidenced by comparisons of monozygotic and dizygotic twins. It is also suspected (but not yet confirmed) that variations in blood pressure may result from the cumulative effects of polymorphisms in several genes that affect blood pressure; for example, some studies have associated hypertension with sequence variants in both the angiotensinogen and the angiotensin receptor genes. This is why blood pressure tends to worsen with age.

Reduced renal sodium excretion in the presence of normal arterial pressure may be a key initiating event in essential hypertension. Sustained hypertension requires the participation of the kidney, which normally responds to hypertension by eliminating sodium. Water follows salt, and natriuresis is diuresis. Ventricular work and especially right atrial stretch results in the release of natriuretic hormones (BNP, ANP). In established hypertension, both increased blood volume and increased peripheral resistance contribute to increased blood pressure. Decreased sodium excretion may sequentially lead to increases in fluid volume and cardiac output, and the baroreceptors respond with peripheral vasoconstriction, thereby elevating blood pressure. At the higher blood pressure, enough additional sodium is excreted by the kidneys to equal intake and prevent further fluid retention. Thus, a new steady state of sodium balance is achieved ("resetting of pressure natriuresis"), but at the expense of increased blood pressure.

Vasoconstrictive influences are α_1 stimulation by the sympathetic nervous system and angiotensin 2 (Ang 2), which "tenses the angios," from the RAAS. This increases systemic vascular resistance. The increased systemic vascular resistance should increase the GFR, and "pressure natriuresis" should correct the excess blood volume. This theory of pressure natriuresis is untested and uncertain.

Environmental factors, such as stress, obesity, cigarette smoking, physical inactivity, and heavy salt consumption, are all implicated in hypertension. Unexpectedly, **alcohol consumption**, which acts as a diuretic, is associated with hypertension. The key to hypertension's mechanism of pathogenesis is not completely understood, but interventions to reduce blood pressure and improve the chronic diseases it causes are well understood. We'll talk about those in the next lesson (Hemodynamics #6: *Hypertension Pharmacology*).

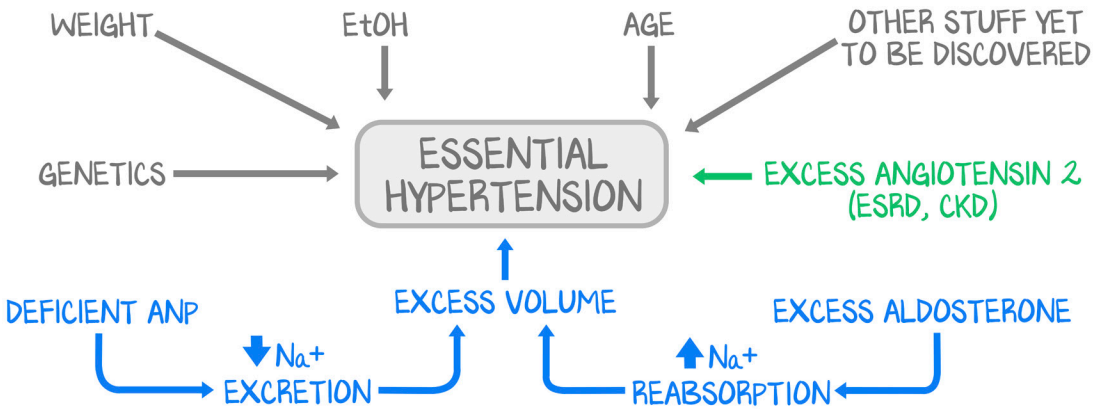

Figure 5.2: Essential Hypertension
Multifactorial approach to hypertension pathogenesis. The sympathetics clamp down on blood vessels. The RAAS increases volume. Increased volume produces a stronger force of contraction. Baroreceptors sense this and vasoconstrict with more sympathetics. The sympathetics clamp down on the vasculature and stimulate renin release. And so the cycle continues.

Essential Hypertension

You will not be responsible for staging hypertension in the Basic Sciences. This is about mechanisms, not management. But you are responsible for understanding the mechanisms of action of antihypertensives and which part of the MAP equation they influence. This is a preview of essential hypertension.

STAGE	SYS	DIA	INITIAL TX
Normal	< 120	< 80	Lifestyle
Elevated BP	> 120	< 80	Lifestyle
Stage 1	> 130	> 80	Lifestyle 1 med
Stage 2	> 140	> 90	Lifestyle 2 meds
Urgency	> 180	> 110	IV then PO
Emergency	Evidence of end-organ damage		MAP 25% reduction in 6 hours

LIFESTYLE	LABEL	GOAL
Diet	Low Na^+ DASH High K^+	< 2.4 g NaCl Fruits, citrus
EtOH	Men Women	2 drinks/day 1 drink/day
Exercise	Cardio	30 min/day 2.5 hours/week
Weight loss	BMI < 25	

Table 5.1: Stages of HTN

Hypertensive urgency is any blood pressure > 180 systolic or > 110 diastolic without evidence of end-organ damage. It is an acute condition in which a person normally has control of their blood pressure but is then seen with very elevated levels. This can be as simple as not taking their blood pressure medications. This is seen in the clinic, urgent care, or emergency department. It's managed with oral medications (sometimes with intravenous medications or topical agents to bring the pressure down while the oral medications start to take effect). A person can have blood pressure greater than 180/110 and be at their baseline, so not in hypertensive urgency. At this stage in your training, 120/80 is good, 180/110 is catastrophically high.

Hypertensive emergency is any blood pressure > 180 systolic or > 110 diastolic with evidence of end-organ damage. And it can be anything—chest pain, elevated serum markers for any organ in dysfunction, papilledema—that makes it a hypertensive emergency. Hypertensive emergency is treated in the intensive care unit with an infusion of titratable blood pressure agents. The goal is to use intravenous nitrates or calcium-channel blockers to reduce the MAP by 25% in the first 2–6 hours, then reduce it to normal ranges with oral medications within 24 hours. Oral medications are initiated with the infusion, and the infusion is titrated to ensure that the MAP is not too rapidly dropped (which could cause a stroke).

Vascular Changes

Two histological changes can be seen in patients with hypertension. We're giving you both the old nomenclature and the new, so you can be certain that you know what each means should you encounter either form. We are not being thorough regarding all possible changes to the vasculature. We will do that in CAD #1: *Pathophysiology of Atherosclerosis*. The two histological changes in this lesson are specifically associated with hypertension.

The **benign** vascular change is **hyaline arteriolosclerosis**. You saw this in Hemodynamics #3: *Aorta*. It was called benign because it wasn't the histological changes seen in the diagnosis of malignant hypertension. Because the name "malignant hypertension" has been replaced by "hypertensive emergency," you need not call hyperplastic arteriolosclerosis benign. Hyaline arteriolosclerosis is a histological finding. This is frustrating because the words do not mean what they mean as English words. In English, hyaline describes something that is translucent, like glass or the sky, and sclerosis means hardening. In hyaline arteriolosclerosis, there is protein deposition into the endothelial wall, between the cells and their basement membrane. The protein does not have nuclei, and the protein is extracellular. With an H&E stain, the protein is pink, amorphous, and continuous. That pink, amorphous, and continuous protein is what **hyaline** means in the language of histology. You cannot see through it, it isn't translucent . . . it just doesn't have any nuclei in it. Because the protein is between the cells and the basement membrane, as it accumulates, it pushes the endothelial cells farther and farther toward the center of the lumen, as evidenced by the location of their nuclei—really close together and where the lumen should be. The loss of luminal radius is what **sclerosis** means in the language of histology. Because it is happening to arterioles, it gets the name **hyaline arteriolosclerosis**.

Said simply, high blood pressure causes damage to the endothelial cells. When damaged, they leak protein. The protein accumulates within the tunica media. A puddle of protein accumulates all around the circumference of the arteriole. The longer the high blood pressure damages the endothelial cells, the more protein is leaked, and the bigger the puddle gets. The cells are identifiable on histology by their basophilic (blue) nuclei. The amorphous and continuous puddle of protein is pink. You will also learn in the Endocrine module that diabetes does this to the arterioles as well, but for now, associate hyaline arteriolosclerosis with chronic hypertension.

Hyperplastic arteriolosclerosis is synonymous with **malignant hypertension**. Because the clinical condition "malignant hypertension" has been replaced by "hypertensive emergency," and one episode of hypertensive emergency will not give you the histological finding of hyperplastic arteriolosclerosis, malignant hypertension is now a histological diagnosis, indicative of very high, very out-of-control blood pressure for a long time. The histological finding is best identified when staining for the basement membrane. There will be constant duplication of the basement membrane, appearing as concentric rings that eventually obliterate the lumen. This term now likely represents clinical hypertensive emergency and histological hyperplastic arteriolosclerosis and should be considered no longer valid. But licensing exams use it so often that we could not eliminate it from the text entirely. The concentric rings are often referred to as **onion-skinning** or onion-skin fibrosis (both unhelpful terms, as "concentric rings of duplicated basement membrane" is more descriptive, and there is no fibrosis, merely hyaline and sclerosis).

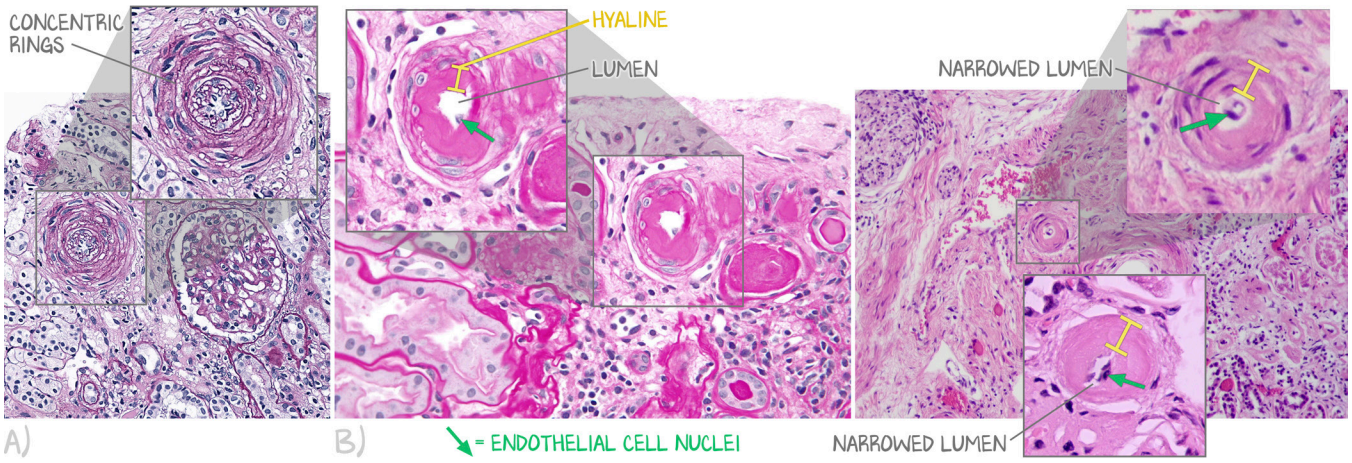

Figure 5.3: Small Vessel Changes in Hypertension
(a) Hyperplastic arteriolosclerosis in a kidney (the glomerulus is to the right). The blood vessel is occluded with multiple circular rings representing duplication of the basement membrane. (b) Various samples at different magnifications demonstrating the pink, amorphous stuff surrounding the lumen of small arterioles.

We're going to do this again in CAD #1: *Pathophysiology of Atherosclerosis,* where we talk about even more types of vascular sclerosis. For now, **concentric rings** means "malignant hypertension," and **pink amorphous stuff** means "chronic hypertension."

Hypertensive Heart Disease

Just as this lesson simplified vascular changes, it also avoids a detailed discussion of the mechanisms of hypertensive heart disease. There are very specific cellular changes that define the type of hypertrophy that skeletal muscles undergo (defined for you in Structure and Function #6: *Heart Failure*). Here, you only need to see that the heart is a muscle, and if you make it work harder, it will get bigger and beefier.

If you go to the gym and do biceps curls week after week, your biceps get bigger. Skeletal muscle is G_0 tissue, so it cannot hypertrophy through hyperplasia. Instead, skeletal muscle gets bigger via cellular hypertrophy. Cardiac muscle is G_0 and responds to "heavier weight"—hypertension (**increased afterload**)—by getting bigger—myocyte hypertrophy. The individual myocytes get bigger by adding sarcomeres. The cardiac muscle gets bigger and stronger. Because the entire left ventricle feels the resistance of afterload equally, there will be a uniform hypertrophy of the left ventricle—all the way around. Fatter myocytes mean thicker ventricular wall. Hypertensive heart disease is essentially synonymous with diastolic heart failure (heart failure with preserved ejection fraction)—the thicker, stronger myocardium becomes equally noncompliant. Treating hypertension prevents this hypertrophy.

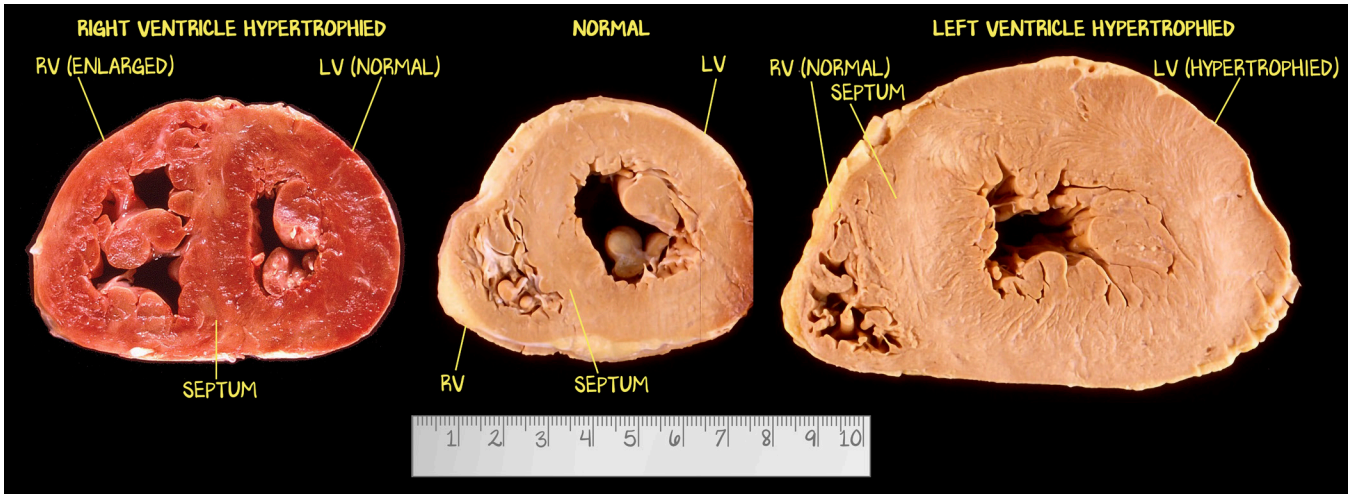

Figure 5.4: Hypertensive Heart Disease
Cross-sections of hearts comparing the relative increase in size from normal depending on the original insult. In isolated right ventricular hypertrophy (cor pulmonale), the right and left ventricles cannot be discerned from one another, both appearing equal in size. The right side of the image is the right ventricle. In isolated left ventricular hypertrophy (systemic hypertension, aortic stenosis), the left ventricle is massively thickened, with barely any lumen.

Systemic hypertension causes left ventricular hypertrophy. Pulmonary hypertension causes right ventricular hypertrophy. Pulmonary arterial pressures only reach 15 mmHg; 20 mmHg is considered pulmonary hypertension. The right ventricle is naturally less beefy than the left because it spends its life beating against a small resistance. The most common cause of pulmonary hypertension is left heart failure. When isolated to the right heart, the term is **cor pulmonale**. The ventricle that feels the pressure is the one that grows bigger. When pulmonary hypertension develops, the **right heart hypertrophies**.

You're going to get more detail in subsequent lessons. Hypertension is far more a clinical game in choosing the right combination of antihypertensives based on comorbidities than a well-elucidated pathogenetic problem. Almost certainly within your practice lifetime, developments will arise that determine there is indeed no such thing as essential hypertension, but rather multiple hypertensions—all presenting with elevated blood pressure but responding to individualized medication and lifestyle interventions. We just haven't found the genes, the alleles, or the means to deduce what is what.

Secondary Hypertension

HHHARP CO ("Triple Harp Company") is an advanced organizer that Dr. Williams created to keep track of the causes of secondary hypertension. This is not essential hypertension, but rather high blood pressure with a correctable cause, often surgical. You will not need to know how to work up a patient with secondary hypertension in the Basic Sciences, and the mechanisms that these conditions cause are not yet known to you. You will see them throughout the course, and this should serve as a catalog for those conditions. When you are in the Clinical Sciences, we go over these conditions in the context of refractory hypertension—high blood pressure despite multiple blood pressure agents.

DIAGNOSIS	MECHANISM	CLINICAL FEATURES
Hyperaldosteronism (primary)	Renin-independent autonomous secretion of aldosterone by the adrenal gland	Hypertension and hypokalemia
Hyperthyroidism	Excess thyroid hormone	Proptosis, eyelid lag, heat intolerance, tachycardia, weight loss
Hypercalcemia	Acute hypercalcemia causes contraction of smooth muscles and acts as a pressor	Nonspecific; routine lab work shows an elevated level
Aortic coarctation	Disproportionate blood flow to the upper extremities	Rib notching, cold legs, hypertensive arms *or* Claudication in babies learning to walk
Renovascular (secondary)	Renin-driven secretion of aldosterone by the adrenal gland	Young woman = fibromuscular dysplasia *or* Old man = renal artery stenosis
Pheochromocytoma	Epinephrine-secreting adrenal gland tumor	Pallor, Palpitations, Pain, Perspiration, Pressure
Cushing's	Glucocorticoid-secreting tumor	Diabetes, buffalo hump, moon facies, hypertension
Obstructive sleep apnea	Not well understood	Daytime somnolence, snoring, frequent apneic spells while asleep, obesity

Table 5.2: Secondary Hypertension
Triple Harp Company, the mechanisms of secondary hypertension, and the clinical features that drive the diseases. Do not memorize this table, merely familiarize yourself with it.

Citations

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